SYSTEM AND METHOD FOR ENABLING SIMULTANEOUS CALIBRATION AND IMAGING OF A MEDIUM

CROSS-REFERENCE TO A RELATED APPLICATION

[0001]   This application claims priority from the Provisional Appln. No. 60/261,492 filed on January 12, 2001, the entire disclosure of which is incorporated herein by reference.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002]   This invention was made with Government support under grants from the National Institutes of Health, NIH R29-NS38842 and NIH P41-RR14075, and the U.S. Army, No. DAMD17-99-2-9001. As a result, the Government of the United States of America has certain rights to the invention.

TECHNICAL FIELD

[0003]   The invention relates to imaging, and more particularly to calibration of optical methods of imaging highly scattering media.

BACKGROUND

[0004]   Opaque media such as paint, milk, foam, emulsions, colloidal suspensions and human tissue do not strongly absorb visible light, while being optically turbid. This turbidity is a result of a very short scattering length characteristic of photons traveling

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within these media. The light does not travel in straight lines through such substances, and instead "diffuses" in a manner similar to heat flow. In other words, photons are multiply scattered within these media until they are either absorbed, or they exit the boundaries of the medium.

[0005]   Recently, there has been a significant interest in the use of optical radiation for imaging within the highly scattering media, such as a biological tissue. Photons can travel within a highly scattering medium along a distribution of paths, of which very few are straight. Thus, the direction of the light into a highly scattering medium and a subsequent direction of the diffuse light emitted from the medium provides certain information regarding local variations in the scattering and absorption coefficients. Such information can identify, for example, a breast or brain tumor, bleeding in the brain, or aneurysm. Furthermore, multiple wavelengths can be used to spectroscopically determine local tissue concentrations of oxy-hemoglobin (HbO) and deoxy-hemoglobin (Hb) in tissue, which can vary in response to some stimulus, e.g., a drug. For a general description of such applications, see, e.g., A. Yodh et al., Physics Today, 34-40, March 1995.

[0006]   If the spatially varying optical properties of a highly scattering medium are known, photon propagation within the medium can be calculated numerically. This numerical calculation is simplified when the scattering is much larger than the absorption, in which case photon propagation can be approximated as a diffusion process. This condition is typically satisfied in a biological tissue in the spectral range of about

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700 to 900 nm. The numerical calculation gives the distribution of light inside a highly scattering medium, and is usually referred to as the "forward calculation." For a medium being imaged, however, the "inverse calculation" should be solved, e.g., by deducing the distribution of optical properties within the medium from the diffuse light measurements. Numerical techniques for performing the inverse calculation include singular value decomposition (SVD), simultaneous iterative reconstruction technique (SIRT), K-space diffraction tomography, and a use of an extended Kaman filter. For a general review of techniques for the forward and inverse calculations, see, e.g., S.R. Arridge, *Inverse Problems*, 15:841, 1999.

[0007] In the art of diffuse optical tomography ("DOT"), multiple sources sequentially direct the light into a highly scattering medium (e.g., tissue), at spatially separated locations. For each such source, multiple detectors on the tissue measure the diffuse light emitted from the sample at spatially separated locations. The detectors may further obtain one or more parameters of the diffuse light emitted, e.g., fluence, and then utilize those parameters as input in the inverse calculation. However, the measurements can include various errors caused by, for example, source and detector coupling to the tissue, source and detector positional uncertainties, fluctuations in the source power, and variations in the detector gain.

[0008] to minimize these uncertainties, DOT systems are typically calibrated with initial measurements for a known sample, and the calibration is used to correct the subsequent measurements for imaging an unknown sample. Unfortunately, errors can

vary from a measurement to another measurement because of, e.g., the movement or perspiration of a patient or the movement of an optical fiber that forms part of a source or detector. Thus, the results of an inverse calculation can include experimental systematic errors caused by measurement variations that are independent of the medium's properties of interest. The experimental systematic errors can also limit absolute spectroscopic measurements of the optical properties at a particular spatial location, i.e., absolute, rather than relative, values of absorption and scattering.

[0009] International Application No. WO 01/19241 describes a calibration methodology for the diffuse optical measurements that corrects the transmittance measurements between a source and a detector for factors unrelated to sample properties. The calibration methodology is based on the same set of transmittance measurements that are subsequently corrected by the calibration, and then are used in imaging and/or spectroscopy applications. This calibration method involves a forward calculation for each of multiple source-detector pairs based on an approximate model of the sample, and a minimization of an expression that depends on the forward calculations and the transmittance measurements to determine self-consistent coupling coefficients for every source-detector pair. Once the coupling coefficients are determined, they are used to correct the transmittance measurements. An inverse calculation is performed on the corrected sample measurements to determine spatial variations in the optical properties of the sample.

SUMMARY OF THE INVENTION

[0010] The present invention is preferably based on the fact that by allowing source and detector calibration factors to vary freely in the inverse calculation and be determined simultaneously with image reconstruction, image artifacts can be significantly reduced.

[0011] In general, the present invention provides systems and methods for determining a distribution of one or more optical properties of a medium illuminated with radiation (e.g., electromagnetic radiation, infrared radiation, continuous-waive radiation etc.) from one or more sources, where the radiation exiting the medium is received by one or more detectors. The detectors may be adapted to obtain one or more parameters of the received radiation. Once the radiation is received and the parameters are obtained, one or more optical properties of the medium can be derived using at least one calibration factor and the received radiation, in which the calibration factors are variables. For a highly-scattering medium, the probability that photons entering the medium will scatter can significantly exceed the probability that photons entering the medium will be absorbed. Hence, employing diffusion approximation may be appropriate because the probability of scattering is at least an order of magnitude higher than the probability of absorption. Each source can be spatially separated from a respective detector, e.g. by two centimeters, and the separation selected can be limited by the experimental parameters (e.g., the number of sources and detectors, the radiation used, the size of the medium

- 5 -

etc.). Where the medium is human tissue, the separation may be one or more centimeters.

[0012] The calibration factors used as variables in deriving one or more optical properties of the medium can include, for example, a source coupling factor, (which can be referred to interchangeably with a source strength or a detector gain), a detector coupling factor, a detector gain, a source location factor, and a detector location factor.

[0013] The optical properties may be derived as a continuous-wave data and include, e.g., the absorption and scattering. However, the optical properties may also be derived, for example, as a frequency-domain or time-domain data. In case that the derived optical properties are in the frequency domain, each would have a respective amplitude and phase. Alternatively, if the derived optical properties are in the time domain, each would have a respective amplitude and temporal off-set.

[0014] The or more of these optical properties can be derived by solving an inverse problem. The inverse problem can be solved by using, for example, a linear approximation model. One such exemplary linear approximation model used to derive the optical properties of the medium is a Born Approximation. Another exemplary linear approximation model is a Rytov Approximation. In the Rytov Approximation model, the measured parameter (e.g., fluence), is defined as an exponential of a perturbation on the background fluence. A specific implementation of an embodiment of the method of the present invention using the Rytov approximation involves minimizing a least-squares expression for the difference between the logarithms of the theoretical and measured

- 6 -

fluence for each source-detector pair. The model can also scale the obtained parameters taken as input (e.g. fluence), to make those parameters dimensionless and to be on the same order as the calibration factors.

[0015]   Some examples of the property distributions obtained from performing the calculations on these measured parameters may include an absorption distribution, a scattering distribution, a distribution of both, etc. The determined property distribution can be displayed in one or more images.

[0016]   In another embodiment of the present invention, a computer-readable medium containing a program is provided that can cause a processor to receive radiation scattered through an illuminated medium as input. Also, the processor may be programmed so as to obtain one or more parameters of the received radiation as input. The program can further cause the processor to derive one or more optical properties of the medium by using the input and one or more calibration factors. The program can subsequently cause the processor to determine a property distribution using the derived optical properties. The property distribution may be provided as output. The program can use a non-linear or linear model to derive the optical properties of the media. Using the Rytov approximation model, the least-squares expression for the difference between the logarithms of the theoretical and measured fluence for each source-detector pair can be minimized so as to derive the optical properties, and determine the property distribution. The program can also scale all obtained parameters taken as input to make

- 7 -

them dimensionless and to be of the same order as the freely varying source and detector calibration factors.

[0017] In yet another embodiment of the present invention, systems are provided for determining the distribution of one or more optical properties of a medium illuminated with radiation from one or more sources. These systems have one or more radiation detectors for receiving radiation. These systems also include a processor for deriving one or more optical properties from the received radiation and one or more calibration factors. The processor also determines the distribution using one or more properties of the medium.

[0018] The sources can have optical fibers and lasers, and the detectors may include optical fibers linked to photodetectors. To irradiate the medium, the system can use electromagnetic radiation, e.g., infrared radiation, or any continuous-wave radiation. The sources providing the radiation can be spatially separated from the detectors that receive the radiation. The spatially separated sources can extend in a plane opposite to a plane containing the detectors, and the spatial separation can be, e.g., two centimeters, and can be varied according to the experimental parameters (i.e., the number of sources and detectors, the radiation used, and the size of the medium). When the medium is human tissue, the separation can be one or more centimeters. The processor can also provide absorption coefficients, scattering coefficients, or both.

[0019] In addition, the property distribution determined by the system of the present invention can be provided as an image on a display, e.g., a computer screen. The

model used to determine the property distribution can again be non-linear or linear. One such model includes the Rytov approximation and can involve, e.g., minimizing the square of the difference between the logarithms of the theoretical and measured fluence for each source-detector pair. The model can also utilize scaling parameters obtained from the signal as input to make them dimensionless and to be of the same order as the calibration factors.

[0020]   in still another embodiment of the present invention, systems are provided for determining a distribution of one or more optical properties of a medium illuminated with radiation from one or more sources. These systems have means for receiving radiation exiting the medium, and means for deriving one or more optical properties of the medium using one or more calibration factors and the received radiation, in which the calibration factors are variables. Means for determining a distribution in the medium using the derived optical properties are also provided.

[0021]   In yet another embodiment of the present invention, software systems are provided which, when executed on a processing device, may determine a distribution of one or more optical properties in a medium illuminated with radiation from one or more sources. These systems have a processing subsystem which, when executed on the processing device, configures the processing device to obtain parameters of received radiation exiting the medium, derive one or more optical properties of the medium using one or more calibration factors and obtained parameters, in which the calibration factors

are variables, and determine a distribution in the medium using one or more derived optical properties.

[0022]   Unless otherwise defined, all technical and scientific terms used herein have the same, or substantially similar, meaning as commonly understood by one of ordinary skill in the art to which the present invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, exemplary methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and are in no way limiting. All cited references are incorporated herein by reference.

[0023]   In prior art systems and methods, several potential experimental systematic errors can hamper the ability to obtain images of the distribution of properties within a medium by applying radiation. While the characteristics of a system can be modeled prior to experimentation, slight fluctuations during experimentation, including for example changes in source strength or detector gain, can cause significant image artifacts. By including calibration in the image reconstruction algorithm, the present invention provides a substantial image improvement, despite the presence of possible considerable experimental systematic errors. One advantage of the methods and systems of the present invention is their ability to obtain diffuse optical tomography images having considerably reduced artifacts. The new imaging methods of the present invention can also be applied in electrical impedance tomography. These imaging methods can be utilized to image spatially varying optical properties of biological media,

e.g., tissue, with enhanced contrast. In addition, such novel methods can be applied to image non-biological media (e.g., plastics, ceramics, or liquids) to detect defects or impurities using radiation. Other features and advantages of the invention will be apparent from the following detailed description, and from the claims. According to the present invention, the source and detector calibration factors can be allowed to vary freely in the inverse calculation and be determined simultaneously with image reconstruction, and thus image artifacts can be significantly reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024]   FIG. 1 is a top-level block diagram illustrating an exemplary embodiment of a method according to the present invention.

[0025]   FIG. 2 is a more detailed block diagram illustrating a step of deriving optical properties of the method shown in FIG. 1.

[0026]   FIG. 3 is a schematic diagram of an exemplary embodiment of a diffuse optical tomography system according to the present invention.

[0027]   FIG. 4 is a schematic diagram of an exemplary source-detector pair for the system of FIG 1.

[0028]   FIG. 5 is a diagram of a first example of an experimental geometry derived using the present invention.

[0029]   FIGS. 6A, 6B and 6C are exemplary images of simulated data obtained from the experimental geometry in FIG. 5 generated for 0%, 40% and 80% uncertainties,

respectively, using a normalized Rytov approximation and excluding the reconstruction of freely varying source and detector coupling factors.

[0030]   FIGS. 6D, 6E and 6F are exemplary images of simulated data obtained from the experimental geometry in FIG. 5 generated for 0%, 40% and 80% uncertainties, respectively, using a normalized Rytov approximation and including the reconstruction of freely varying source and detector coupling factors.

[0031]   FIGS. 7A, 7B, 7C and 7D are images of simulated data obtained from the experimental geometry in FIG. 5 generated for 0%, 40%, 80% and 120% uncertainties, respectively, using a Born approximation and including the reconstruction of freely varying source and detector coupling factors.

[0032]   FIGS. 7E and 7F are images of simulated data obtained from the experimental geometry in FIG. 5 generated for 80% and 120% uncertainties, respectively, using a normalized Rytov approximation and including the reconstruction of freely varying source and detector coupling factors.

[0033]   FIGS. 8A, 8B, 8C, and 8D are images, similar to those of FIGS 7A-7F, of simulated data obtained from the experimental geometry in FIG. 5 generated for 10%, 20%, 40% and 60% uncertainties, respectively, using a Rytov approximation with the reconstruction of freely varying source and detector coupling factors, but without the normalization.

[0034]   FIG. 9A is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 0.1 mm

using a normalized Rytov approximation and excluding the reconstruction of freely varying source and detector location factors.

[0035]   FIG. 9B is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 0.1 mm using a normalized Rytov approximation and including the reconstruction of freely varying source and detector location factors.

[0036]   FIG. 10A is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 0.5 mm using a normalized Rytov approximation and excluding the reconstruction of freely varying source and detector location factors.

[0037]   FIG. 10B is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 0.5 mm using a normalized Rytov approximation and including the reconstruction of freely varying source and detector location factors.

[0038]   FIG. 11A is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 1.0 mm using a normalized Rytov approximation and excluding the reconstruction of freely varying source and detector location factors.

[0039]   FIG. 11B is a set of images of simulated data obtained from the experimental geometry in FIG. 5, generated for localization uncertainty of e.g., 1.0 mm

using a normalized Rytov approximation and including the reconstruction of freely varying source and detector location factors.

[0040]   FIG. 12 is an example of the experimental setup of the system according to the present invention.

[0041]   FIG. 13A is a set of images of data obtained from the experiment of FIGS. 9A and 9B using a normalized Rytov approximation excluding the reconstruction of freely varying source and detector calibration factors.

[0042]   FIG. 13B is a set of images of data obtained from the experiment of FIGS. 9A and 9B using a normalized Rytov approximation including the reconstruction of freely varying source and detector calibration factors.

DETAILED DESCRIPTION

[0043]   The novel methods of the present invention calibrate sources and detectors as part of the inverse calculation for image reconstruction to reduce image artifacts.

General Methodology

[0044]   Research in diffuse optical tomography has rapidly progressed in moving the imaging modality from the development stage of computer simulations and phantom experiments to the application stage of imaging animal and human subjects. However, little work has discussed the importance and solution of experimental details that degrade image quality including, without limitation, the treatment of boundary conditions for solving the forward problem, source and detector coupling to tissue, source and detector

- 14 -

positional uncertainties, and intrinsic tissue heterogeneity. The novel calibration

techniques according to the present invention are based on the principle that, e.g., the

inclusion of calibration factors as variables in the image reconstruction algorithm

significantly improves the image quality.

[0045]   The calibration techniques of the present invention can be applied to

determine a property distribution within a scattering medium, which is an ill-posed, non-

linear inverse problem. A linear approximation can be obtained by assuming the

variations may be described as small perturbations in absorption and scattering, $\delta\mu_\alpha$ and

$\delta\mu_s$', respectively, around known background values of absorption and scattering, $\mu_{\alpha o}$

and μ_{so}', respectively. As indicated previously, one or more parameters of diffuse light

emitted through a scattering medium may be obtained and used as input in the inverse

calculation. One of those parameters is preferably fluence. A linear approximation of the

measured fluence Φ can be obtained as a perturbation Φ_{pert} on a background fluence Φ_0.

In imaging, the fluence Φ is measured experimentally and the perturbation Φ_{pert} (which is

caused by spatial variation in the radiative properties of the sample) should preferably be

calculated.

[0046]   An accurate determination of the perturbation Φ_{pert} prefers a calibration of

a source and a detector, and a reasonable estimate of the background fluence Φ_0. Errors

in the determination of the calibration factors are likely to result in a highly localized

absorption and scattering perturbations appearing adjacent to the sources and detectors as

a compensation for the errors in the image reconstruction process. This type of image

- 15 -

NY02:364961.1

noise can be evidenced by high frequency spikes appearing preferentially near source and detector locations.

[0047]   The exemplary methods of the present invention allow for the calibration by enabling the calibration factors to vary freely in the inverse calculation, and determining them as part of the image reconstruction algorithm. There are various calibration factors, e.g., source and detector coupling factors s and d, respectively, and source and detector location factors r_s and r_d , respectively. By considering the logarithm of the measured fluence Φ as input into the image reconstruction algorithm, the perturbation Φ_{pert} becomes linearly dependent on the logarithms of s and d. However, the perturbation Φ_{pert} can remain non-linearly dependent on the optical properties of the sample. To obtain a linear dependence on the optical properties, an approximation, e.g., the Rytov or Born approximation, can be used, and the problem thus can become completely linear.

The Forward Problem:

[0048]   The radiative transport equation provides a rigorous theory to describe radiation emitted from a medium. It may be applied to the migration of photons through highly scattering media, such as biological tissue. This approach can indicate that near-infrared photons in highly scattering media e.g., human and animal tissue, essentially undergo a random walk, since the scattering probability greatly exceeds the absorption probability. The propagation of these photons through a highly scattering medium can

- 16 -

therefore be described by a diffusion approximation to the radiative transport equation. This exemplary diffusion can be provided as an equation as follows:

$$-\nabla \cdot (D(\mathbf{r})\nabla\Phi(\mathbf{r},t)) + v\mu_\alpha(\mathbf{r})\Phi(\mathbf{r},t) + \frac{\partial\Phi(\mathbf{r},t)}{\partial t} = vS(\mathbf{r},t),$$ (1)

where $D(\mathbf{r})$ is the photon diffusion coefficient, $\Phi(\mathbf{r},t)$ is the photon fluence at position r and time t, v is the speed of light in the medium, $\mu_\alpha(\mathbf{r})$ is the absorption coefficient, and $S(\mathbf{r},t)$ is the source distribution of photons (see, e.g., A. Ishimaru, *Wave Propagation and Scattering in Random Media*, Academic Press, Inc. San Diego, 1978; M. S. Patterson et al., *Applied Optics* 28:2331, 1989; R. C. Haskell et al., *Journal of the Optical Society of America A*, 11:2727, 1994). The photon diffusion coefficient $D(\mathbf{r})$ is defined by the equation:

$$D(\mathbf{r}) = \frac{v}{3\mu_s'(\mathbf{r}) + \alpha\,\mu_\alpha(r)},$$ (2)

where $\mu_s'(\mathbf{r})$ is the reduced scattering coefficient. The coefficient α can be variously set to three, zero, or some other value (see, e.g., D. J. Durian, *Optics Letters*, 23:1502, 1998; R. Aronson and N. Corngold, *Journal of the Optical Society of America A*, 16:1066, 1999).

[0049]   When focusing on the variations in the absorption, the value selected for α is moot, and therefore it can preferably be set to zero.

[0050]   When the distribution of properties within the medium varies spatially, two approaches can be used to find approximate solutions to Equation (1): the Born approximation (see, e.g., A. Ishimaru, *Wave Propagation and Scattering in Random*

Media, Academic Press, Inc. San Diego, 1978; A. C. Kak and M. Slaney, *Principles of Computerized Tomographic Imaging*, IEEE Press, New York, 1988), and the Rytov approximation (see, e.g., A. C. Kak and M. Slaney, *Principles of Computerized Tomographic Imaging*, IEEE Press, New York, 1988). The Born approximation can preferably be defined as:

$$\Phi = \Phi_o + \Phi_{pert}. \tag{3}$$

The Rytov approximation is preferably :

$$\Phi = \Phi_o \exp(\Phi_{pert}). \tag{4}$$

[0051]   Each approach decomposes the total fluence Φ into the background fluence Φ_o, which only depends on the background optical properties $\mu_{\alpha o}$ and μ_{so}', and Φ_{pert}, which is linearly related to the spatial variations in the optical properties $\delta\mu_\alpha$ and $\delta\mu_s$. For the Rytov approximation, assuming absorption variations only, the perturbation can be calculated as follows:

$$\Phi_{pert}(\mathbf{r}_s, \mathbf{r}_d) = -\frac{1}{\Phi_o(\mathbf{r}_s, \mathbf{r}_d)} \int \Phi_o(\mathbf{r}_s, \mathbf{r}) \frac{v\delta\mu_\alpha(\mathbf{r})}{D_o} G(\mathbf{r}, \mathbf{r}_d) d\mathbf{r}, \tag{5}$$

where $\mathbf{r}_s$ and $\mathbf{r}_d$ are the respective positions of the source and detector, D_o is the diffusion coefficient for the chosen α, and G is the Green's function of the photon diffusion equation for the background optical properties provided by the boundary conditions. If the background is homogeneous, G can be expressed analytically for some simple geometries (see, e.g., M. S. Patterson et al., *Applied Optics* <u>28</u>:2331, 1989; R C. Haskell

- 18 -

et al., *Journal of the Optical Society of America A*, <u>11</u>:2727, 1994; S. R. Arridge et al.,

Physics in Medicine and Biology, <u>37</u>:1531, 1992).

[0052]   One exemplary geometry to which Equation (4) can be applied is a slab,

i.e., a geometry where the sources are in a single plane on one side of the sample and the

detectors are in a plane on the opposite side thereof. In this geometry, the extrapolated

zero-boundary condition can be applied to the above-described radiative transport

problem to solve for the Green's function *G* of the diffusion equation for the background

optical properties (see, e.g., R. C. Haskell et al., *Journal of the Optical Society of*

America A, <u>11</u>:2727, 1994). The background fluence Φ_0 is related to the Green's function

by the source and detector coupling factors. The source coupling factor *s* includes source

power and a coupling to the medium. The detector coupling factor *d* includes detector

gain and a coupling to the medium. Using *s* and *d* respectively, to represent the source

and detector coupling factors, the background fluence is as follows:

$$\Phi_o(\mathbf{r}_s, \mathbf{r}_d) = s\, d\, G(\mathbf{r}_s, \mathbf{r}_d) \tag{6}$$

The Inverse Problem:

[0053]   By solving the inverse problem, the images of spatially varying optical

properties can be generated from measurements of the fluence Φ. The inverse problem

includes solving a least-squares equation. For the Rytov approximation, the expression to

minimize can be as follows:

$$F(x) = \sum_{i=1}^{N_{meas}} \left[\ln \Phi_{Theory,i}(x) - \ln \Phi_{Meas,i} \right]^2 , \tag{7}$$

where the index i is summed over the measurements for each source-detector pair, $\Phi_i(x)$ is provided by Equations (4) and (5) where x is a vector giving $\delta\mu_\alpha$ at each voxel position, and $\Phi_{Meas}(x)$ is the measured fluence for each source-detector pair.

[0054]   For the case of fewer measurements than unknowns, the linear problem is underdetermined, and can be described by the (regularized) Moore-Penrose generalized inverse:

$$\hat{x} = -A^T \left(AA^T + \lambda I \right)^{-1} y, \tag{8}$$

where I is the identity matrix, and λ is the Tikhonov regularization parameter. Each element of the matrix A can be defined as:

$$A_{i,j} = -\frac{v}{D_o \Phi_o\left(\mathbf{r}_{s,i}, \mathbf{r}_{d,i}\right)} \Phi_o\left(\mathbf{r}_{s,i}, \mathbf{r}_j\right) G\left(\mathbf{r}_j, \mathbf{r}_{d,i}\right), \tag{9}$$

where $\mathbf{r}_{s,i}$ and $\mathbf{r}_{d,i}$ are the positions of the ith source and the ith detector, respectively. The position of the jth voxel is expressed as $\mathbf{r}_j$. Using the Rytov approximation, each element of y can be as follows:

$$y_i = \ln\left[\frac{\Phi\left(\mathbf{r}_{s,i}, \mathbf{r}_{d,i}\right)}{\Phi_o\left(\mathbf{r}_{s,i}, \mathbf{r}_{d,i}\right)} \right]. \tag{10}$$

[0055]   In one exemplary approach, λ can be set to 10^{-3} of the maximum eigenvalue of AA^T (see, e.g., H. Dehghani et al., *Physiological Measurement*, 20:87, 1999; V. Kolehmainen et al., *Physiological Measurement*, 18:289, 1997).

- 20 -

Image and Calibration Factor Reconstruction

CALIBRATION FOR THE SOURCE AND DETECTOR
COUPLING FACTORS AND IMAGE RECONSTRUCTION

[0056] Image quality depends on accurate knowledge of the background optical properties, $\mu_{\alpha o}$ and μ_{so}', and the source and detector calibration factors s and d. Therefore, estimates of the matrices **A** and **y** similarly depend on these quantities. By considering $\mu_{\alpha o}$ and μ_{so}' as known properties, the inverse problem can be solved for the calibration factors.

[0057] As described above, the measurements can include various errors caused by, for example, source and detector coupling to the medium, fluctuations in source power, variations in detector gain, and source and detector positional uncertainties. Hence, the measurements can be calibrated for the source and detector coupling and intensity fluctuations (source and detector coupling factors), as well as for their positions (source and detector location factors).

[0058] In the case when measurements should be calibrated for the source and detector coupling factors s and d (the source and detector coupling and fluctuations in the source power and the detector gain), an augmented model of a particular measurement, y_i may be written in terms of the unknown source coupling factors s_k, the detector coupling factors d_l, and the absorption perturbations $\delta\mu_{\alpha j}$. The source and detector coupling factors can preferably refer to both coupling fluctuations and intensity fluctuations of the

- 21 -

sources and detectors. Using these variables, the particular measured parameter (in this case fluence) may be expressed as follows:

$$y_i = \ln\left[\frac{\Phi(\mathbf{r}_{s,i}, \mathbf{r}_{d,i})}{\Phi_o(\mathbf{r}_{s,i}, \mathbf{r}_{d,i})}\right] = \ln[s_{k(i)}] + \ln[d_{l(i)}] + \sum_j A_{i,j}\delta\mu_{\alpha,j},$$ (11)

where $k(i)$ and $l(i)$ identify the source and detector, respectively, which are used for the ith measurement.

[0059]   In case that numerous measurements are conducted, the measured parameter (fluence) can be written in a matrix form as:

$$\mathbf{y} = \mathbf{B}\xi, \text{ where } \mathbf{B} = [\tilde{\mathbf{A}}\,\mathbf{S}\,\mathbf{D}],$$ (12)

where $\mathbf{S}$ is a source coupling factor matrix, $\mathbf{D}$ is a detector coupling factor matrix, and $\tilde{\mathbf{A}}$ is a matrix $\mathbf{A}$ rescaled by a factor of $\mu_{\alpha o}$.

Factor ξ is defined by the formula:

$$\xi = \left[\frac{\delta\mu_{\alpha,1}}{\mu_{ao}} \cdots \frac{\delta\mu_{\alpha,N_v}}{\mu_{\alpha o}} \ln s_1 \cdots \ln s_{N_s} \cdots \ln d_1 \cdots \ln d_{N_d}\right],$$ (13)

where N_v is the number of voxels, N_s is the number of sources, and N_d is the number of detectors. $\delta\mu_{\alpha j}$ can be scaled by $\mu_{\alpha o}$ to make the elements dimensionless and being of the same order as $\ln s$ and $\ln d$. Scaling these quantities to make them dimensionless and of the same order as the logarithms of the calibration parameters yields a normalized formulation.

[0060]   As indicated previously, $\tilde{\mathbf{A}}$ is a rescaling of the matrix $\mathbf{A}$ whose terms are defined by Equation (9) by a factor of $\mu_{\alpha o}$. Thus,

$$\widetilde{\mathbf{A}} = \mu_{\alpha o} \, \mathbf{A}. \tag{14}$$

[0061] Matrices **S** and **D** have block diagonal form. For example, **S** has a one in the kth column for each measurement corresponding to source k, and **D** has a one in the lth column for each measurement corresponding to detector l. Thus, with four measurements between two sources and two detectors, the following matrix is defined:

$$[\mathbf{S} \quad \mathbf{D}] = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 \end{bmatrix}$$

CALIBRATION FOR THE SOURCE AND DETECTOR LOCATION FACTORS AND IMAGE RECONSTRUCTION

[0062] Conversely, if the measurements should be calibrated for the source and detector locations, an augmented model of a particular measurement, y_i, may be defined in terms of the uncertain source location δr_{sk}, uncertain detector location δr_{dk} and the absorption perturbations $\delta\mu_{aj}$. In this exemplary augmented model, y_i may be expressed as:

$$
y_i = \ln\left[\frac{\Phi\left(r_{s,k(i)}, r_{d,l(i)}\right)}{\Phi_o\left(r_{s,k(i)}, r_{d,l(i)}\right)}\right] = \left[\frac{1}{\Phi_o\left(r_{s,k(i)}, r_{d,l(i)}\right)}\right] \nabla_{s,k(i)} \Phi\left(r_{s,k(i)}, r_{d,l(i)}\right) \bullet \delta r_{s,k(i)}
$$
$$
+ \frac{1}{\Phi_o\left(r_{s,k(i)}, r_{d,l(i)}\right)} \nabla_{d,l(i)} \Phi\left(r_{s,k(i)}, r_{d,l(i)}\right) \bullet \delta r_{d,l(i)} + \sum_j A_{i,j} \delta\mu_{\alpha,j}, \tag{15}
$$

where $k(i)$ and $l(i)$ identify the source and detector, respectively, used for the ith measurement. It should be noted that δr_{sk} and δr_{dl} represent the differences from the

- 23 -

respective assumed values as used in Φ_0 and the real values for the measurement of Φ. In addition, δr_{sk} and δr_{dl} can be vector quantities representing the uncertainties in the x, y, and z coordinates of the corresponding source or detector.

[0063]   For this exemplary embodiment of the present invention, in case that numerous measurements are conducted, the measured parameter (fluence) can be written in a matrix form as follows:

$$y = B\xi, \text{ where } B = [\tilde{A} \; P_s \; P_d] \tag{16}$$

where ξ is defined by:

$$\xi = \left[\frac{\delta\mu_{\alpha,l}}{\mu_{ao}} \; \cdots \; \frac{\delta\mu_{\alpha,N_v}}{\mu_{\alpha o}} \; \frac{\delta r_{s,1}}{\sigma} \; \cdots \; \frac{\delta r_{s,N_s}}{\sigma} \; \frac{\delta r_{d,1}}{\sigma} \; \cdots \; \frac{\delta r_{d,N_d}}{\sigma} \right] \tag{17}$$

in which N_v is the number of voxels, N_s is the number of sources, and N_d is the number of detectors. Scaling $\delta\mu_{\alpha j}$ by $\mu_{\alpha o}$ and the positional unknowns by σ makes the elements dimensionless. σ can be selected so as to make the unknowns of the same order of magnitude, and in this manner, σ is preferably an estimate of the expected error in the source and detector locations. Similarly, $\tilde{A}$ is a rescaling of the matrix A whose terms are given by Equation (9) by a factor of $\mu_{\alpha o}$. Thus,

$$\tilde{A} = \mu_{\alpha o} A. \tag{18}$$

[0064]   Matrices P_s and P_d can have a block diagonal form. For example, P_s may be non-zero in the kth column for each measurement corresponding to source k, and P_d may be non-zero in the lth column for each measurement corresponding to detector l. These preferably have the same form as the [S D] matrix provided above with respect to

- 24 -

the image reconstruction including the calibration for the source and detector coupling factors.

Frequency Domain Formulation

[0065] The imaging method according to the present invention is not limited to using continuous-wave radiation. In the frequency domain, the measured parameters of amplitude and phase may also be obtained. If the measured parameters are in the frequency domain, then, for example, the source and detector coupling factors have corresponding unknown phases θ_s and θ_d, respectively. They also likely have unknown amplitudes A_s and A_d. The $\ln s$ and $\ln d$, which appear in Equation (13), can be complex, as are the corresponding elements in the matrix $\mathbf{A}$. To separate the real and imaginary portions of the complex matrix, the real portions can be stacked on top of the imaginary portions, i.e.,

$$B = \begin{bmatrix} re(\tilde{A}) & re(S) & re(D) \\ im(\tilde{A}) & im(S) & im(D) \end{bmatrix}. \tag{19}$$

[0066] In the frequency domain, should be adjusted as follows:

$$\xi = \begin{bmatrix} \dfrac{\delta\mu_{\alpha,1}}{\mu_{\alpha o}} & \cdots & \dfrac{\delta\mu_{\alpha,N_v}}{\mu_{\alpha o}} & \ln A_{s_1} & \cdots & \ln A_{N_s} \theta_{s_1} & \cdots & \theta_{N_s} & \ln A_{d_1} & \cdots & \ln A_{d_{N_s}} & \theta_{d_1} & \cdots & \theta_{N_d} \end{bmatrix}. \tag{20}$$

[0067]   For the case of four measurements between two sources and two detectors, the complex matrix can be:

$$[\mathbf{S}\ \ \mathbf{D}]=\begin{bmatrix} 1 & 0 & i & 0 & 1 & 0 & i & 0 \\ 1 & 0 & i & 0 & 1 & 0 & i & 0 \\ 0 & 1 & 0 & i & 0 & 1 & 0 & i \\ 0 & 1 & 0 & i & 0 & 1 & 0 & i \end{bmatrix} \tag{21}$$

[0068]   The example of a formulation for the case where there are uncertain source and detector locations si substantially similar to the example provided above. In particular, Equation (19) would be provided as follows:

$$\mathbf{B}=\begin{bmatrix} \mathrm{re}\big(\widetilde{A}\big) & \mathrm{re}(P_S) & \mathrm{re}(P_D) \\ \mathrm{im}(\widetilde{A}) & \mathrm{im}(P_S) & \mathrm{im}(P_D) \end{bmatrix}. \tag{22}$$

Time Domain Formulation

[0069]   The imaging method according to the present invention can also be applied to measurements taken in the time domain. To obtain time domain data, each source provides a temporally coherent pulse of radiation, e.g., a picosecond light pulse, and the detectors are time-gated to measure the temporal delay of the radiation in addition to its intensity. For a general reference on such time-domain techniques in diffuse optical tomography see, e.g., M.S. Patterson et al., *Applied Optics* 28:2331, 1989; S.R. Arridge, *Inverse Problems*, 15:841, 1999. Therefore, to apply the new calibration methods to time-domain data, the calibration factors *s* and *d* are described by corresponding unknown amplitudes and temporal off-sets. The unknown amplitudes in the time-domain are treated in the same fashion as in the continuous-wave domain. The unknown

- 26 -

temporal off-sets represent a non-linear perturbation and can be reconstructed using a non-linear form of the model.

[0070]   The example of a formulation for the case where there are uncertain source and detector locations si substantially similar to the example provided above.

Exemplary Illustrations of the System and Method of the Present Invention

[0071]   Referring to FIG. 1, a top-level block diagram presenting an exemplary embodiment of a method according to the present invention is illustrated. Initially, the radiation which exits from the medium is received (step 110). Then, in step 120, one or more optical properties of the medium are derived using the radiation received in step 110 and one or more calibration factors, wherein the calibration factors are variables. Subsequently, in step 130, a distribution of the optical properties in the medium is determined using the optical properties derived in step 120. The details of steps 110 - 130 are described in detail herein above.

[0072]   Further details for step 120 of deriving one or more optical properties of the medium are additionally illustrated in FIG. 2 and described below. In particular, parameters of radiation are obtained in step 210. One of such parameters can be fluence. The detectors with which the radiation exiting the medium is received may be adapted to directly measure the parameters of the radiation, e.g., fluence. Alternatively, the parameters may be calculated using the data corresponding to the received radiation. Once the parameters are obtained in step 210, the formulation of each obtained parameter can be augmented to include the calibration factors as variables (step 220). As described

above, the calibration factors may include the source coupling factor, detector coupling factor, source location factor and detector location factor. Subsequent to augmenting the formulations of the obtained parameters of radiation, one or more optical properties of the medium are derived as output by solving an inverse problem in which the augmented formulations are used as input (step 230).

General System

[0073]   FIG. 3 shows an exemplary embodiment of the system capable of executing the method according to the present invention in which experimental systematic errors may cause significant image artifacts. Such system can be a diffuse optical tomography ("DOT") system 300. The system 300 includes an array of spatially separated light sources 310 and spatially separated detectors 320. During use, the array of sources 310 and detectors 320 can be positioned over a sample 350 to be imaged, e.g., a patient's head or breast. A controller 330 connected to the light sources 310 can sequentially trigger them to forward or provide light into the sample 350, so that a highly scattering medium may cause the light to become diffuse within the sample. For each sequentially triggered source, each detector 320 receives light that reaches it through sample 350 to obtain the measured fluence Φ. The controller 330 is also connected to the detectors 320, and selectively channels the signals from the detectors 320. An analyzer 340 is connected to the controller 330 and analyzes the signals generated by detectors 320.

[0074]   For example, in one exemplary embodiment shown in FIG. 4, each source

310 may include a diode laser 400 for producing optical radiation and a lens 420 for

coupling the optical radiation into an optical fiber 410. The optical fiber 410 has an end

415 adjacent to the sample 450 for directing the optical radiation into the sample 450.

Each detector 420 includes an optical fiber 452 having an end 455 adjacent to the sample

450 for receiving the optical radiation exiting the sample 450, a photodetector 460 for

measuring the intensity of the optical radiation received by the optical fiber 452, and an

amplifier 470 for amplifying the output of the photodetector 460.

[0075]   To obtain information about the optical properties of the sample 450 from

the fluence, it is preferable to consider the measured fluence Φ as representing the

perturbation Φ_{pert} on a background fluence Φ_0. According to Equation (4), this can be

accomplished by using the Rytov approximation. By minimizing the least-squares

expression as provided in Equation (7), the analyzer 340 can simultaneously obtain the

optical properties of the sample and conduct source and detector calibration.

[0076]   In other embodiments of the present invention, the light source can include

a laser other than a diode laser, e.g., an ultrafast laser, or may be an incoherent source.

Also, the sources can include a common light source that selectively couples light into

multiple fibers that deliver the light to spatially separated locations on the sample.

Alternatively, the sources need not include optical fibers at all. For example, the lasers

themselves can be positioned adjacent to the sample or can include beam delivery optics

- 29 -

to direct the light to the sample through free space. Furthermore, the light sources can provide light at multiple wavelengths by including, for example, multiple diode lasers.

[0077]   In the description provided below, it can be assumed that the sources provide continuous-wave optical radiation, and that the detectors measure the intensity of the optical radiation.

[0078]   It should be understood that the calibration techniques described herein can also be applied to other measurement techniques in which the sources do not provide continuous-wave radiation. For example, in some techniques, the amplitude of optical radiation provided by the sources can be modulated to create photon density waves in the sample, and the detectors are configured to measure the amplitude and phase of the photon density waves after propagation through the sample. For a general reference on "DOT" techniques with modulated optical radiation, see, e.g., M.A. O'Leary et al., *Phys. Rev. Lett.* 69, 2658 (1992). Furthermore, in other techniques, each source can provide a temporally coherent light pulse, for example, a picosecond pulse, and the detectors may be time-gated to measure the temporal delay of the diffuse light pulse in addition to its intensity. For a general reference on such time-domain DOT techniques, see, e.g., M.S. Patterson et al., *Appl. Opt.* 28:2331, 1989, and S.R. Arridge, *Inverse Problems*, 15:841, 1999.

Exemplary Applications

[0079]   The methods and systems of the present invention provide the ability to obtain images of spatially varying optical properties within highly scattering media, such

as human and animal tissue, and can therefore be used to address many new biomedical problems and applications. For example, these novel methods and systems can be used to image a region of tissue to ascertain the presence of an early tumor, a small amount of bleeding, or an early aneurysm. In another exemplary application, multiple wavelengths can be used to evaluate local tissue concentrations of chemicals, such as hemoglobin, within tissue. Also, the methods and systems of the present invention can be further combined with use of a chemical stimulus to determine the chemical response.

[0080] Non-biomedical applications for the methods and systems of the present invention also exist and can be used to image materials such as plastics, ceramics, and liquids for defects or impurities. In addition, the methods and systems of the present invention can be used for identifying regions of interest having distinct optical properties within highly scattering media, such as concealed objects, without invasive study of that media. For example, the methods of the present invention can be used to image an optical heterogeneity within a diffusive liquid. Furthermore, the novel calibration methods and systems can also be applied in electrical impedance tomography.

Software Implementation

[0081] The calibration methods can be implemented in hardware, software, or a combination of both. The methods can be implemented via computer programs using standard programming techniques following the methods, equations, and Figures described herein. Program code can be executed using a processing arrangement which can receive input data to perform the functions described herein and generate output

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information. The output information can be applied to one or more output devices, such as a display monitor, printer etc.

[0082]   Each program can preferably be implemented in a high-level procedural or object-oriented programming language to communicate with a general computer system. However, the programs can be implemented in assembly or machine language, if desired. In any case, the computer language can be a compiled or interpreted language.

[0083]   Each computer program can preferably be stored on a storage medium or device (e.g., ROM, magnetic diskette, or optical disc) readable by a general or special purpose programmable processing arrangement, for configuring and operating the computer when the storage media or device is read by the processing arrangement to perform the procedures and techniques described herein. The computer program can also reside in cache or main memory during program execution. The processing methods can also be implemented as a computer-readable storage medium, configured with a computer program, where the storage medium so configured can cause the processing arrangement to operate in a specific and predefined manner so as to perform the functions and techniques described herein.

[0084]   For example, referring again to FIG. 3, the analyzer 340 includes a processor 370, an input/output control card 360, a user interface 390 such as a keyboard and monitor, and memory 380. The memory 380 stores a program 385 specifying the steps of the calibration method. When executed, the program 385 causes the processor 370 to carry out the steps of the method according to the present invention.

- 32 -

EXAMPLES

[0085]   The methods and systems of the present invention are further described in the following examples, which do not limit the scope of the invention described in the claims and are provided merely for illustrative purposes.

Example 1 — Simulation of Image Reconstruction

[0086]   Several advantages of the methods of the present invention were demonstrated by simulations. The results obtained utilizing a normalized Rytov approximation without the reconstruction of calibration factors (i.e., without using the new calibration methods), a normalized Rytov approximation with reconstruction, a Born approximation with reconstruction, and a Rytov approximation without normalization were compared. A diagram of a first example of an experimental geometry is shown in FIG. 5.

[0087]   The computer simulation involved the transmission through a 6-cm thick slab with background optical properties $\mu_{so}' = 10$ cm^{-1} and $\mu_{ao,} = 0.15$ cm^{-1}. A 1.6-cm diameter absorbing object 550 with $\mu_{so}' = 10$ cm^{-1} and $\mu_{ao} = 0.15$ cm^{-1} was centered at (x, y, z) = (1, -1, 3) cm. Sixteen sources 510 were programmed in a four-by-four grid at z = 0, spaced 2 cm apart to span x = -3 to 3 cm and y = -3 to 3 cm. Similarly, sixteen detectors 520 were located in a four-by-four grid at z = 6, spanning x = -3 to 3 cm and y = -3 to 3 cm in 2-cm steps. All simulated measurements were made with continuous-wave sources.

- 33 -

[0088]   The Full Born expansion was used to solve the forward problem. A 1.6 x

1.6 x 1.6 cm cube 555 divided into 7 x 7 x 7 voxels was centered over the 1.6-cm

diameter absorbing object 550.

[0089]   Initially, the source and detector coupling factors were varied, namely, the

source and detector amplitudes. The source and detector amplitudes were chosen

randomly from a normal distribution with a mean of 1. The effect of different standard

deviations (0%, 40%, and 80%) was investigated. The normal distribution was biased by

discarding negative amplitudes. A separate instance of the source and detector amplitude

variation was considered for each standard deviation. There was no additive

measurement noise (i.e., shot noise or electronic noise) in the simulated data, just the

model error associated with the source and detector amplitudes.

[0090]   For the inverse problem, voxel centers were distributed from x = -3 to 3

and y = -3 to 3 in 0.5-cm steps and z = 0.5 to 5.5 in 0.5-cm steps. There were 1859

voxels, each with dimensions of 0.5 x 0.5 x 0.5 cm. The source and detector amplitudes

were assumed to be all equal to 1. Two different inverse problems were considered: (1)

Rytov without coupling, and (2) Rytov with coupling. In each case, Tikhonov

regularization was used to obtain the pseudo-inverse, since the system matrix is under-

determined and ill-conditioned.

[0091]   FIGS. 6A - 6F show the results obtained with the normalized Rytov

approximation both excluding the reconstruction of the source and detectors coupling

factors (FIGS 6A-6C), and including such factors (FIGS. 6D-6F). FIGS. 6A and 6D

- 34 -

show results for 0% uncertainty in source and detector strengths, FIGS. 6B and 6E depict

images for 40% uncertainty, and FIGS. 6C and 6F reflect 80% uncertainty. All images

span X and Y from -3 to 3 cm, and Z-slices are vertically arranged from 0.5 (top) to 5.5

cm (bottom).

[0092]   The results in FIGS. 6A - 6C show images without the reconstruction of

the source and detectors coupling factors, i.e., the effect of neglecting experimental

systematic errors in the calibration. With no variance (i.e., no systematic error in the

sources and detectors), the object is localized to the correct voxel in X and Y and is

within 1 voxel (0.5 cm) in Z. The amplitude of the object is slightly underestimated due

to blurring. While it is expected that $\delta\mu_a = 0.10$ cm^{-1}, the reconstruction yields $\delta\mu_a =$

0.098 cm^{-1}. The image contains artifacts near the sources and detectors. These artifacts

disappear when the Born approximation is used for the forward problem, indicating that it

arises from mismatch between the exact forward solution and the Rytov approximation

for the inverse model (i.e., it results from model noise unrelated to source and detector

calibration factors).

[0093]   As the standard deviation in the calibration factors increases from FIG. 6A

to FIG. 6C, it is still possible to ascertain the object, but this deviation has reduced the

contrast relative to the surrounding voxels, and its amplitude is smaller than that in the

voxels closest to the sources and detectors. The artifact amplitudes may greatly exceed

the displayed contrast, and have been truncated to preserve contrast sensitivity sufficient

to reveal the object of interest. The model noise caused by an incorrect calibration of the

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source and detector calibration factors (i.e. systematic errors in s and d) clearly degrades the image quality by increasing the artifacts.

[0094]   FIGS. 6D - 6F show the reconstruction results where the source and detector coupling factors are simultaneously determined with the optical properties of the sample using the novel calibration methods of the present invention. Without the variance in the calibration factors, the location of the object remains properly resolved in X and Y coordinates and is within 0.5 cm in Z coordinate. The resolution in FIGS. 6D - 6F, with the simultaneous reconstruction of the calibration factors, is poorer than in FIGS. 6A - 6C, due to its lacking this simultaneous reconstruction. The presence of more unknowns in the inverse calculation using simultaneous reconstruction explains the decrease in the resolution. By contrast, the artifact shown in FIG. 6A due to the error between the exact and the Rytov approximation to the forward problem is reduced using the simultaneous reconstruction. The reconstruction appears to compensate for the model mismatch in the Rytov approximation.

[0095]   Comparing the images generated using the simultaneous reconstruction of the source and detector coupling factors (shown in FIGS. 6D - 6F) to the corresponding images generated without reconstruction (shown in FIGS. 6A - 6C) reveals a significantly improved image quality using the reconstruction. For both 40% and 80% variance, the image quality using the reconstruction in fact remains as good as the case where there is no variance. The minor differences are masked within the contrast sensitivity. While the reconstruction may not accurately determine the independent source and detector

- 36 -

coupling factors with the sample, it assists with the accurate determination of the source-detector coefficient products (e.g., $s_k d_l$) for each measurement. Despite the uncertainties of 80%, the results shown in FIG. 6D - 6F indicate that the source-detector coefficient products can be determined within an accuracy of a few percent. In addition, it has been observed that, when additive shot or electronic measurement noise is included in the simulation, there may be a greater sensitivity to the measurement noise as the source and detector variance increases.

[0096]   FIGS. 7A – 7F show images of simulated data obtained from the experimental geometry in FIG. 5 generated for 0%, 40%, 80% and 120% uncertainties, respectively, using a Born approximation including the reconstruction of freely varying source and detector coupling factors. FIGS. 7E and 7F are images of simulated data obtained from the experimental geometry in FIG. 5 generated for 80% and 120% uncertainties, respectively, using a normalized Rytov approximation including the reconstruction of freely varying source and detector coupling factors. FIGS. 7A - 7F are useful to compare use of the Born approximation with the reconstruction of the source and detector coupling factors to use of the normalized Rytov approximation with the reconstruction. FIGS. 7A - 7D show results for 0% uncertainty to 120% uncertainty in the source and detector strengths. By comparison, FIGS. 7E and 7F depict images for 80% and 120% uncertainty using the Rytov approximation. The Z-slices are vertically arranged with each image spanning X and Y axes from -3 to 3 cm.

[0097]   Images generated using the Born approximation are clearly inferior to those generated using the Rytov approximation for the same level of uncertainty. Indeed, the images generated using the Rytov approximation for uncertainties of 80% (FIG. 7E) and 120% (FIG. 7F) resemble those generated using the Born approximation at 0% (FIG. 7A) and 40% uncertainty (FIG. 7B) more than images using the Born approximation at a comparable level of uncertainty (FIGS. 7C and 7D). The standard Born implementation of the image reconstruction problem is non-linear with respect to the source and detector coupling factors. Therefore, if the initial estimate for the coupling factors is off by more than approximately 10%, simultaneously solving for the coupling factors may not lead to an improved result. By using the Rytov implementation (i.e., taking the logarithm of the data), the dependence on the source and detector factors is made linear, and it is then possible to accurately reconstruct the coupling factors despite an initial guess, possibly off by several hundred percent.

[0100]   While merely substituting the Rytov approximation for the Born approximation offers an improved image quality, the normalization of the different factors in the inverse calculation (i.e., absorption, scattering, and calibration factors) can also contribute to the enhanced image quality. The normalization has a beneficial effect because the reconstruction of several different factors simultaneously is difficult if the factors differ in magnitude by an appreciable amount. Using the normalization, the reconstruction can proceed accurately over a larger range of values. FIGS. 8A - 8D show the exemplary images using the Rytov approximation with the reconstruction of the

source and detector coupling factors, but without the normalization. FIG. 8A shows the results for 10% uncertainty, FIG. 8B for 20%, FIG. 8C for 40%, and FIG. 8D for 60%: FIGS. 8A - 8D have the same X-Y scale and arrangement of Z slices as in FIGS. 7A to 7F for an ease of comparison. Comparing FIGS. 8A - 8D with FIGS. 7E and 7F reveals that normalizing results in the improved image quality, even at higher levels of uncertainty.

[0101]   Alternatively, a different set of calibration factors may be varied. For example, the source and detector locations may be varied randomly with a normal distribution with a mean of 0. The effect of different distribution widths (0.1, 0.5, and 1.0 mm) was investigated. A separate instance of the source and detector amplitude variation was considered for each distribution width. There was no additive measurement noise (i.e. a source or detector electronic noise) in the simulated data, and only the model error associated with the source and detector locations was added.

[0102]   For the inverse problem, voxel centers were distributed from x=-3 to 3 and y=-3 to 3 in 0.5 cm steps and z=0.5 to 5.5 in 0.5 cm steps. Approximately 1859 voxels were provided with dimensions of 0.5 x 0.5 x 0.5 cm. The vector ξ in Equation (14) was initialized to zeros. Two different inverse problems were considered: (1) the Rytov approximation without the localization, and (2) the Rytov approximation with the localization. In each case, the Tikhonov regularization was used to obtain the pseudo-inverse since the system matrix was under-determined and ill-conditioned.

[0103]   FIGS. 9A-11B illustrate the results obtained with the Rytov approximation

excluding and including the reconstruction of the coupling coefficients for optode

localization errors of 0.1, 0.5 and 1.0 mm, respectively. Referring to FIGS. 9A and 9B,

the images of the simulated data obtained from the experimental geometry shown in FIG.

5 using a normalized Rytov approximation excluding and including the reconstruction of

freely varying source and detector location factors, are illustrated for localization

uncertainty of 0.1 mm. With the localization error of 0.1 mm, it is possible to locate the

position of the absorbing heterogeneity despite the presence of image speckle near the top

and bottom surfaces of the scattering medium.

[0104]   With the localization errors of 0.5 mm and greater (See FIGS. 10A and

10B, and FIGS. 11A and 11B, the surface speckle noise obscures the presence of the

absorbing heterogeneity. The speckle noise may arise directly from the localization error.

In most, if not all, cases, including the calibration of optode location in the inverse

problem significantly reduces the surface speckle noise revealing the absorbing object.

Example 2 — Phantom Results

[0105]   The actual image results of a phantom have also been obtained, and FIG.

12 shows the experimental setup for imaging the phantom. A phantom box 1210 has a

set of sources and a set of detectors on its top and bottom plates, respectively. The

phantom box 1210 is connected with an RF Imager 1230 with a set of detector fibers

1220. The phantom box 1210 is also connected with a controller 1280 via a set of source

fibers 1270. A processing arrangement 1290 is coupled with the controller 1280. The phantom box 1210 is further coupled with a beaker 1240 and a pump 1250.

[0106]   The phantom box 1210 was filled with 0.5% intralipid solution, and a 2-cm diameter heterogeneity sphere was embedded in this solution. The content of the sphere was controlled by the circulation channel outside the phantom box 1210, which included the pump 1250 and the beaker 1240 for ink titration. In the experiment, a slab geometry was formed, with the slab having a thickness of 5.11 cm. The center of the ball was located 2.35 cm from the bottom of the slab. There were sources on the top plate ($z = 0$ cm) and detectors on the bottom plate ($z = 5.11$ cm). The signal to the sources was delivered via the source fibers 1270. The signal was light with a wavelength of 830 nm and was modulated at 70 MHz. The amplitude and phase of the diffusely transmitted light were measured. Data was collected from the detectors via the detector fibers 1220 into the radio frequency imager 1230. The processing arrangement 1290 processed the results and generated the images.

[0107]   The images were first generated using the Rytov approximation both excluding and including the reconstruction of the source and detector coupling factors. Images were median filtered using standard techniques because this was found effective in removing speckle artifacts. FIG. 13A shows the images obtained excluding the reconstruction of the source and detector coupling factors, and FIG. 13B shows the images generated including the reconstruction. The X and Y ranges are in centimeters, and Z-slices are vertically arranged from 0.01 (top left) to 5.501 cm (bottom right) in

0.50-cm steps. It is observed that including reconstruction of the source and detector coupling factors improves image quality. In particular, the detail of the heterogeneity sphere can be seen in FIG. 13B for Z=2.01 to Z=3.51 cm, but it may not be observable over the corresponding Z-range in FIG. 13A.

[0108]   It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.